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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,259	07/09/2004	Shunichi Shiozawa	61646 (70904)	7532

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EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/16/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/501,259	SHIOZAWA ET AL.	
	Examiner	Art Unit	
	Steven C. Pohnert	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *1-3,5,6,9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,7 and 8* is/are rejected.

7)☒ Claim(s) *4* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/30/2005, 10/8/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group 3, claims 4 , 7 and 8, in the reply filed on 8/25/2006 is acknowledged. The traversal is on the ground(s) that, "the groups specified in the restriction should not impose an undue burden." This is not found persuasive because the application is a national stage application of a PCT, and under the PCT rules a lack of unity is required for proper restriction. It is noted however that a search burden does exist, in that searching for any single distinct invention of groups 1 to 6 would not result in finding art on the other groups. As such searching for more than 1 of the recited groups would result in a serious search burden.

The requirement is still deemed proper and is therefore made FINAL.

Claim Objections

2. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 4 does not pass the infringement test. Claims 1 and 2 are drawn to the whole gene, while claim 4 only requires the detection of the mutation. As claim 4 does not require all the limitations of claims 1 and 2 it is improperly dependent.

3. Claim 8 is objected to because of the following informalities: the claim recites "highly possibly or has high possibility". The claim is thus not grammatically correct. 5Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 4, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claim 4 encompass a method of evaluating the possibility of onset or onset of rheumatoid arthritis (RA), by detecting the insertion of glycine in the protein of SEQ ID NO. 1 or insertion of "GGT" into SEQ ID NO. 2 in "any" subject or "any" mutation in SEQ ID NO. 1 or SEQ ID NO.2. Claims 7 and 8 are drawn to measuring the amount of mRNA corresponding to SEQ ID NO. 2 with a deletion of "GGT" at position 805. Claim 8 is drawn to the use of threshold values 1 and 2 to determine possibility of a subject developing RA.

The amount of direction or guidance and the Presence and absence of working examples.

The claims are drawn to the insertion of a glycine as the 269th position of SEQ ID NO. 1, or the insertion of "GGT" at nucleotides 805 to 807. However, the data presented in figure 4 of the specification teaches the deletion of 3 nucleotides at position 805. It is unclear from the specification whether the deletion taught in figure 4 of the specification encompasses SEQ ID NO.1 with a glycine at positions 269 and 270, or a glycine at position 269, or no glycine at position 269 or 270, and the nucleic acids that correspond to these proteins.

The specification teaches the insertion of GGT at positions 805-807resulting in a glycine being inserted into amino acid position 269 of SEQ ID NO.1 (see page 25, 1st

full paragraph). The specification further teaches this insertion is depicted in SEQ ID NO. 2 (see page 25, line 10). The specification teaches a 3 base deletion (see page 10, line 11).

The specification teaches the homozygous or heterozygous deletion of "GGT" in SEQ ID NO. 2 occurs in 98.5% of subjects with familial history RA, diagnosed with RA (see Figure 4). The specification further teaches 100% subjects with familial history RA, not diagnosed with RA, were homozygous or heterozygous for deletion of "GGT" in SEQ ID 2 (see figure 4). The specification further teaches 98.2% of subjects with sporadic RA were homozygous or heterozygous for the "GGT" deletion. While 100% of the subjects related to those diagnosed with sporadic arthritis have the homozygous or heterozygous "GGT" deletion.

The specification further teaches the patients that homozygously lack the "GGT" deletion (that have GGT at position 805-807) have RA: familial RA (1.5%) and sporadic RA (1.8%). The specification appears to teach patients that homozygously lack the "GGT" deletion (that have GGT at position 805-807) were found only with RA, but the homozygous or heterozygous "GGT" deletion was found both in subject with RA and those without RA. Thus it appears that an association exists for humans homozygous for the presence of "GGT" at position 805-807.

However, the claims are drawn to the insertion of a glycine as the 269th position of SEQ ID NO. 1 (SEQ ID NO1 teaches a glycine as the 269th amino acid), or the insertion of "GGT" at nucleotides 805 to 807 of SEQ ID NO.2 (SEQ ID NO2 teaches

GGT at positions 05 to 807). It is thus unclear if the applicant wants the invention claimed, or the invention that appears to be taught.

In another study, the specification teaches a statistically significant reduction in mRNA as detected by a probe with sequence of SEQ ID NO.9 in patients (21) with RA compared with 18 controls (see figure 5). The specification does not teach if the RA patients are homozygous or heterozygous for the "GGT" insertion or deletion. Although this finding is statistically significant, the claims require analysis in relation to the first study and the ability to correlate this decreased mRNA with RA however is unclear. The specification further teaches the use of threshold values 1 and 2 to evaluate if a subject is predisposed to RA or not (see page 31, 1st full paragraph). The specification further asserts this value should be set such that value 1 is set to equal or less then the average value of mRNA expression in RA patients (see page 30 1st full paragraph). The specification further asserts threshold value 2 should be set to be equal or more then the average value of mRNA expression for healthy individuals or "arbitrarily in other ways in accordance with the data of detection" (see page 29, lines 12-13).

The specification does not specifically define threshold values for 1 and 2. As the specification asserts threshold values 1 and 2 should be determined by use of averages for RA patients and healthy subjects, or arbitrarily, to evaluate the presence of a disease, let alone the onset of a disease without specific threshold values.

The claims encompasses RA onset in "any" subject, which includes dogs, cats, mice, cows, etc. The specification does not teach that the insertion or deletion claimed

is present in any other species, or that the insertion or deletion would result in RA in any other species.

Claim 4 is broadly interpreted as claiming "any" mutation in SEQ ID NO1 or SEQ ID NO2. The specification does not teach any other mutation in SEQ ID NO 1 or SEQ ID NO2, that results in RA. Further the specification does not how the insertion or deletion in SEQ ID NO1 or SEQ ID NO2 alter function of the gene or protein resulting in RA, so as to enable one of skill in the art to extrapolate from this single mutation in humans to other mutations in humans or other species.

The specification and claims do not convey in clear, concise and exact terms how to make and use the invention.

The state of prior art and the predictability or unpredictability of the art:

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art of Wu (Journal of pathology (2001) volume 195, pages 53-65). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The prior art of Newton et al (Journal of computational biology (2001)

volume 8, pages 37-52) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to determine if the claimed invention encompasses SEQ ID NO.1 with a glycine at positions 269 and 270, or a glycine at position 269, or no glycine at position 269 or 270, and the nucleic acids that correspond to these peptides. Experimentation would be replete with unpredictable trial and error analysis because the specification does not in clear, concise and exact terms describe the invention so as to allow the skilled artisan to make and use the invention as claimed.

The skilled artisan would then have to determine if the insertion as claimed was sufficient for the RA phenotype, or if as the specification asserts the lack of a deletion is correlated with RA. Further the skilled artisan would have to determine if this insertion or deletion taught by the specification is by itself sufficient for diagnosing RA onset, or as the specification shows requires homozygosity of "GGT" at position 805-807. The skilled artisan would further have to determine by unpredictable trial and error experimentation if the insertion/deletion that is taught and claimed is present in dogs, cats, mice and correlated with RA in these species.

The skilled artisan would further have to determine if "any" mutation in SEQ ID No1 or SEQ ID No2 is correlated with RA. This would be unpredictable because the specification has only taught one mutation and the ordinary artisan could not extrapolated a structure function relationship to other mutations with humans or other species from this one example.

Further the skilled artisan would have to determine the threshold values 1 and 2 that would be indicative of expression of mRNA of SEQ ID NO.2 in such a way that as to determine if a patient had high or low expression of this nucleic acid molecule. As the specification does not define threshold values 1 and 2 and suggests they can be arbitrarily determined (see page 29, lines 12-13), it would be unpredictable to use these threshold values to predict a disease state.

Due to the scope of the claims, one of skill in the art would be required to further undertake unpredictable trial and error experimentation to make and use the invention as claimed.

Therefor, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

6. Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in

the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claim 4 encompass "any" mutation of SEQ ID NO.2. The claims do not set forth any functional requirements for mutations of SEQ ID NO.2.

When the claims are analyzed in light of the specification, the invention encompasses an enormous number of nucleotide molecules. The specification teaches the insertion of "GGT" at position 805 to 807 which corresponds to the insertion of glycine at amino acid 269.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been disclosed. The instant specification teaches SEQ ID 2, which is one species in the genus of "any" mutation of SEQ ID NO.2.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification teaches only 1 mutation, which is not representative of the genus claimed. The sequence of the insertion/deletion is not taught in such a way that the skilled artisan could envision the structure claimed. Further, the specification does not teach a relationship between the structure of mutation and functional consequences of this mutation so the skilled artisan could determine from the disclosure of this single insertion/deletion, other associated mutations in humans or other species.

In the instant application, the provided information regarding "any" mutation of SEQ ID NO.2, do not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding "any" mutation of SEQ ID NO.2 is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules the large genus of species encompassed by claim 4.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is indefinite because it lacks a positive active step relating back to the preamble. The preamble recites a method of evaluating the onset or possibility of onset of rheumatoid arthritis, however the last positive active step is drawn to detecting a mutation set forth in claim 1 or 2 . Therefore it is unclear as to whether the method is drawn to evaluating the onset or possibility of onset of rheumatoid arthritis or detecting a mutation set forth in claim 1 or 2.

Claim 4 is indefinite because it is unclear if mutation recited is the mutation of claim1, claim 2, or is "any" mutation. The term "mutation" lacks an article, such as "a" or "the". Accordingly it is unclear if the term refers to a specific mutation or any possible mutation.

Claim 4 is indefinite because it is unclear if the "GGT" to be inserted in SEQ ID NO 2 at nucleotides 805 to 807 results in SEQ ID NO. 2 or if another GGT is required resulting in nucleotides 805 to 810 being "GGTGGT."

Claim 4 is indefinite because it is unclear if the glycine to be inserted as amino acid 269 results in SEQ ID NO. 1, or if another glycine is required resulting in a glycine at 269 and 270.

Claim 7 is indefinite because it lacks a positive active step relating back to the preamble. The preamble recites a method of evaluating the onset or possibility of onset of rheumatoid arthritis, however the last positive active step is drawn to measuring the amount of mRNA derived from a disease susceptibility gene for rheumatoid arthritis. Therefore it is unclear as to whether the method is drawn to evaluating the onset or possibility of onset of rheumatoid arthritis or measuring the amount of mRNA derived from a disease susceptibility gene for rheumatoid arthritis.

Claim 7 recites, "measuring an amount of an expressed mRNA derived from a disease susceptibility gene for rheumatoid arthritis, the gene having a base sequence that is as shown in SEQ. ID NO.2 but deleted of 3 bases "GGT", which are Nos.805 to 807 bases in the sequence." It is unclear if the claim is drawn measuring

mRNA expression of SEQ ID NO. 2 or specifically the expression of mRNA of SEQ ID 2 with the "GGT" deletion.

Claim 7 is indefinite because it is unclear if the "GGT" to be inserted in SEQ ID NO 2 at nucleotides 805 to 807 is the one listed in SEQ ID NO. 2 or if another GGT is required resulting in nucleotides 805 to 810 being "GGTGGT."

Claim 8 is indefinite because threshold values 1 and 2 are not defined in the specification or claims. The skilled artisan would thus be unable to evaluate expression of a mRNA without threshold values to compare it to.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claim 4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis, et al (Cell, (1996) Volume 87, pages 1161-1169).

As noted in the MPEP 211.02, " a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation." In the present

situation, evaluating onset or onset possibility of rheumatoid arthritis (claims 4, 7, 8) and the preamble limitation is not accorded patentable weight. Accordingly, the claim language of evaluating onset or onset possibility of rheumatoid arthritis (claims 4, 7, 8) merely sets forth the intended use or purpose of the claimed methods, but does not limit the scope of the claims.

With regards to claim 3, Davis et al teaches detection of a deletion of a glycine at position 269 (see page 1163, 2nd column, lines 10-15, and figure 3). This is a 3 base deletion corresponding to "GGT" of position 805 to 807.

With regards to claim 7, teaches detection of the three base deletion by RNAse protection assay (see page 1163, 2nd column, lines 13-17). This is interpreted as measuring the amount of expressed mRNA.

Conclusions

No claims are allowed.

Summary

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven C. Pohnert whose telephone number is 571-272-3803. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

JEHANNE SITTON
PRIMARY EXAMINER
11/13/06